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EXAMINER	
MAIER, LEIGH C	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,669	KARLSSON ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005 and 17 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 145-147 have been added. Claims 65-147 are pending. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Any objection or rejection not expressly repeated has been withdrawn.

Claim Rejections - 35 USC § 112 – 1st paragraph

Claims 145-147 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

Claim 145 recites the limitation "wherein the composition contains no ethylene oxide." Claim 146 recites a sterilized composition "wherein the sterilized composition was never subjected to treatment with ethylene oxide, gamma-irradiation, or beta-irradiation." Claim 147 recites a product-by-process claim comprising "providing an unsterilized powder." Applicant states in the remarks that such a powder necessarily lacks the characteristics of a product that has been previously sterilized.

The examiner does not find support for any of these new limitations in the specification.

Claim Rejections - 35 USC § 112 – 2nd paragraph

Claims 145-147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 145 recites the limitation "wherein the composition contains no ethylene oxide." However, the specification does not discuss any method by which ethylene oxide content is to be determined or the limits of detection of any such method. The newly submitted reference, PT-69652, discloses sterilization of micronized steroids by exposure to a gas composition comprising ethylene oxide. By the detection method used in determining the final content of EO, the content is found to be 0 ppm. Of course there may be a few molecules of EO, but they are undetectable. So for all intents and purposes, this product has "no ethylene oxide." For one of ordinary skill to be apprised of the metes and bounds of the claims, the artisan must know how the EO is to be determined, along with the limits of detection of such a method.

Claim 146 recites a sterilized composition "wherein the sterilized composition was never subjected to treatment with ethylene oxide, gamma-irradiation, or beta-irradiation." A product cannot be defined by its history unless some action in said history affects the product in some measurable way to an observer not aware of the history. For example, going back to PT-69652, this reference sterilizes steroids as set forth above. The product has clearly been exposed to EO, but no trace of residual EO can be detected. Therefore, to one observing this product, not knowing its history, it apparently has not been exposed to EO. Furthermore, there is no limitation regarding the amount of exposure. It seems likely that a product could be exposed to any of these, EO or irradiation, for a short enough time to avoid leaving any indication of said exposure.

Claim Rejections - 35 USC § 103

Claims 65-70, 73-80, and 84-93 are again rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of RUBINFELD et al (US 5,824,668) and ANSEL et al (Pharmaceutical Dosage Forms and Drug delivery Systems, 1995), as set forth in the previous Office action.

Applicant's arguments filed August 22, 2005 have been fully considered but they are not persuasive.

Applicant generally discusses what is known in the art about EO sterilization and cites a document, published after Applicant's filing date, which states "The U.S. Food and Drug Administration (FDA) has proposed strict limits on allowable residual products in drugs because of possible mutagenic and carcinogenic properties of ethylene oxide." The document discloses that strict (but not quantified) limits were proposed by the FDA several years after Applicant's filing date. These limits may or may not have been adopted. Applicant also submitted a declaration (Trofast declaration) comprising data from tests to determine residual EO in budesonide samples. However, these data are not particularly relevant without context including any requirements regarding acceptable EO limits for pharmaceuticals at the time of the invention.

Applicant objects to the use of RUBINFELD because the reference does not explicitly discuss warnings regarding the use of EO, whereas PURWAR states that EO sterilization "*probably* would not be allowed to be introduced today due to present day's stringent regulatory requirement for *almost zero* ethylene oxide requirement." (emphasis added) First of all, the emphasis of RUBINFELD is not a process of sterilization, per se, so there is no expectation that

the reference would discuss what is known in the art about this process. However, it is clear evidence that this procedure was an accepted method at the time of the invention. On the other hand, the emphasis of PURWAR *is* the description of a new process of sterilization, as an alternative to the process using EO. As such, PURWAR would clearly be motivated to explicitly accentuate the disadvantages of alternative processes. Finally, PURWAR refers to a non-quantified "almost zero" ethylene oxide requirement. The reference does not state that it is required that a pharmaceutical product have no detectable EO.

Applicant further takes issue with the modification of JAKUPOVIC by the use of a filter size adequate to prepare a sterile product. Applicant contends that filter pore size determines droplet size, which in turn, determines particle size and compare examples 3 and 4. So in going from Example 3 to Example 4, the use of a filter pore size an order of magnitude lower, the particle size decreases 4%, from 2.60 to 2.49. By Applicant's logic, decreasing the size the necessary two more orders of magnitude, the particle size would still be expected to be greater than 2, well within the ranges set forth by JAKUPOVIC and the instant claims. Even so, the "pore size determines droplet size determines particle size" theory seems to be contradicted by the results of Examples 4 and 6.

Applicant further contends that JAKUPOVIC specifies a particular pore size and excludes one small enough for sterilization for a reason. The examiner respectfully disagrees with this premise. The reference states a *preferred* range and does not specifically *exclude* any size. Notably, the reference does not count filter size among those variables affecting particle size. As far as Applicant's hypothesis that a suitable pore size might make the process to slow to be widely practical, the examiner agrees that this is probably the case. However, the claims are

not drawn to a process. As far as the other hypotheses regarding possible outcomes with a filter size suitable for sterilization, (droplet vs. film, etc.) these hypotheses are merely speculation without supporting evidence.

Applicant further discusses at length possible problems with filtration sterilization. The fact that one process may be more cumbersome than another may be persuasive in prosecuting a process claim, but the claims are not drawn to a process. Applicant has merely speculated that the recited product could not be produced by this process. Again, argument is not evidence. The examiner agrees that filter-sterilized product would not contain dead bacteria, whereas heat-sterilized product would. However, the EO sterilized product would also contain dead bacteria.

Claims 65-93 are again rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of RUBINFELD et al (US 5,824,668) and ANSEL et al (Pharmaceutical Dosage Forms and Drug delivery Systems, 1995) and further in view of RADHAKRISHNAN et al (US 5,192,528), as set forth in the previous Office action.

Claims 65-70, 73-80, 84-109, 112-117, 121-123, 127-131, 136-138, and 142-144 are again rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of RUBINFELD et al (US 5,824,668) and ANSEL et al (Pharmaceutical Dosage Forms and Drug delivery Systems, 1995) and further in view of HELZNER (WO 97/01341), as set forth in the previous Office action.

Claims 65-70, 73-80, 84-117, 121-123, 127-131, 136-138, and 142-144 are again rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of RUBINFELD et al (US 5,824,668) and ANSEL et al (Pharmaceutical Dosage Forms and Drug

delivery Systems, 1995) and further in view of HELZNER (WO 97/01341) and GUY et al (US 5,540,930), as set forth in the previous Office action.

Claims 65-70, 73-80, 84-95, 115-120, 124-126, 130-132, and 139-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of RUBINFELD et al (US 5,824,668) and ANSEL et al (Pharmaceutical Dosage Forms and Drug delivery Systems, 1995) in further view of BRATTSAND et al (US 3,992,534).

Applicant submits no additional arguments in response to these rejections.

Claims 65-70, 73-80, 84-93, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of PT-69652 and RUBINFELD et al (US 5,824,668).

The invention is as described in the previous Office action.

JAKUPOVIC teaches as set forth in the previous Office action. JAKUPOVIC does not teach a sterile product.

PT-69652 discloses a process for the sterilization of micronized steroids wherein the final product has negligible—that is, not seen at the limits of detection—content of EO. See entire reference. The examiner maintains that if EO cannot be detected in a product, it has not in effect been "subjected to treatment" with EO.

RUBINFELD teaches as set forth in the previous Office action. This reference establishes that EO sterilization was an accepted method of pharmaceutical sterilization at the time the invention was made.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize the respirable, dry powders disclosed by JAKUPOVIC by either treatment with EO. The artisan would have been motivated to sterilize the respirable particles, to prevent microbial growth in the packaged material meant for administration to patients, with a reasonable expectation of success.

It would also be obvious to the ordinarily skilled worker to purify the glucocorticosteroid (prepare in a form having a high percentage of the glucocorticosteroid by weight) in order to limit contaminants in products for human administration.

With respect to EO sterilization, Applicant cites an FDA document as evidence that EO sterilization would produce a product that is chemically different than the one recited. Applicant further contends that "it appears likely that treatment of budesonide with ethylene oxide to sterilize budesonide will permanently alter some of the budesonide molecules present in the composition." The FDA document states what can happen when residual EO is trapped in packaging with a pharmaceutical product. This implies long-term exposure. It does not describe what will necessarily occur when a pharmaceutical product is exposed to EO in a process, such as that disclosed by PT-69652. Applicant contends that the presence of EO-created contaminants cannot be ruled out without conducting appropriate tests. However, neither can they be proven to be present without such tests. It is noted that the data set forth in the Trofast declaration does not mention the presence of an EO-adduct impurity.

Claims 65-93 and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of PT-69652 and RUBINFELD et al (US 5,824,668) and further in view of RADHAKRISHNAN et al (US 5,192,528).

The invention is as set forth above. Claims 71, 72, and 81-83 recite products having a significant percentage of particle sizes less or equal to about 5 μm.

JAKUPOVIC teaches as set forth above. The aim of the reference is preparation of glucocorticosteroids available to the respiratory tract including the lower area. See page 1, lines 9-15. As noted above, JAKUPOVIC teaches the range of particles of about 0.1 μm to about 10 μm, but the reference does not specifically exemplify particles of less than 5 μm. However, the reference teaches how the size of the particles may be controlled by process parameters that one of ordinary skill would be able to optimize with routine experimentation.

PT-69652 and RUBINFELD teach as set forth above.

RADHAKRISHNAN teaches that corticosteroids, including budesonide, have utility for the treatment of a variety of respiratory disorders. See col 1-2 and col 7, lines 57-63. The reference further teaches that aerosol particles of corticosteroid formulations will be directed to particular sites in the respiratory tract, depending on their size. Particles must be must be less than about 1 μm in order to reach the lower region of the respiratory tract (alveoli). See figure 1 and col 5, lines 37-48.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare glucocorticosteroid in the form of sterile, respirable particles with MMD of less than 1 μm. The artisan would have been motivated to prepare this size in order for the respirable glucocorticosteroid to reach the alveoli during treatment. The artisan would

reasonably expect success in preparing such particles, as JAKUPOVIC had taught how to prepare particles down to about 0.1 μm. The artisan would be motivated to sterilize the product for reasons described above. Purity limitations are addressed above.

Claims 65-70, 73-80, 84-109, 112-117, 121-123, 127-131, 136-138, and 142-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of PT-69652 and RUBINFELD et al (US 5,824,668) and further in view of HELZNER (WO 97/01341).

The invention is as set forth above. Dependents are drawn to suspensions comprising the product of the independent claims and therapeutic methods comprising administration of either the powder or the suspension.

JAKUPOVIC teaches as set forth above. The reference teaches treatment of diseases of the respiratory tract in general, but not the particular disorders recited in the claims. The reference teaches the preparation of pharmaceutical compositions, but not specifically suspensions.

PT-69652 and RUBINFELD teach as set forth above.

HELZNER teaches the preparation of suspensions comprising anti-inflammatory corticosteroids, including budesonide. See abstract and pp 5-8. The reference teaches the addition of a variety of typical pharmaceutical additives, such as those recited in the claims. The reference teaches a preferred pH range of about 4.0 to 6.5. The reference further teaches that these compounds have utility in the treatment of allergic rhinitis.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a sterile suspension comprising the budesonide and having a pH in the recited ranges. The artisan would be motivated to prepare such a suspension for the art-disclosed utility. It would be within the scope of the artisan to select appropriate additives and optimize their concentration through routine optimization.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the dry, sterile glucocorticosteroids or as aqueous suspensions of said glucocorticosteroids for the treatment of the recited respiratory disorders, inflammation, allergies or rhinitis. It would be within the scope of the artisan to optimize the dosage and prepare suspensions of appropriate concentration for said dosage through routine experimentation.

Claims 65-70, 73-80, 84-117, 121-123, 127-131, 136-138, and 142-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of PT-69652 and RUBINFELD et al (US 5,824,668) and further in view of HELZNER (WO 97/01341) and GUY et al (US 5,540,930).

The invention is as set forth above. Claims 110 and 111 require that the suspension comprise EDTA.

JAKUPOVIC, PT-69652 and RUBINFELD teach as set forth above.

HELZNER teaches as set forth above. The reference teaches a variety of additives, including benzalkonium chloride. The reference does not teach a suspension comprising EDTA.

GUY teaches that EDTA—alone or in combination with benzalkonium chloride—has utility in preventing microbial contamination of corticosteroid suspensions. See col 3, lines 35-40; col 4, lines 1-14; and col 5, lines 1-5.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a sterile suspension comprising budesonide as set forth above. It would be further obvious to prepare one comprising EDTA for its utility as an antimicrobial to protect the sterile composition from microbial contamination.

Claims 65-70, 73-80, 84-95, 115-120, 124-126, 130-132, 139-141, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) in view of PT-69652 and RUBINFELD et al (US 5,824,668) in further view of BRATTSAND et al (US 3,992,534).

The invention is as set forth above. Dependents are drawn to suspensions comprising the product of the independent claims and therapeutic methods comprising administration of either the powder or the suspension.

JAKUPOVIC, PT-69652 and RUBINFELD teach as set forth above. The references do not teach the treatment of COPD or asthma.

BRATTSAND teaches that budesonide (compound 12) has utility for the treatment of inflammatory conditions, asthma and obstructive lung disease. See col 12. The reference further teaches the preparation of budesonide in a variety of forms, including suspensions. See composition 8.

It would have been obvious to one having ordinary skill at the time the invention was made to prepare budesonide, in the form of a sterile powder or suspension, as set forth above. One of ordinary skill would be motivated to prepare such a composition for administration to a patient for the treatment of inflammatory disorders, asthma, or obstructive lung disease, such as COPD. The artisan would reasonably expect success in doing so because BRATTSAND had taught that budesonide has this utility.

Claim 147 is rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) and BUSSEY et al (J. Parenter. Sci. Tech., 1983).

Claim 147 is a product-by-process claim. However, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.

JAKUPOVIC teaches as discussed in the previous Office action. JAKUPOVIC does not teach a sterile product.

BUSSEY teaches the sterilization of (gluco)corticosteroid powders by ^{60}Co irradiation. See entire reference, particularly the abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize the respirable, dry powders disclosed by JAKUPOVIC by either irradiation. The artisan would have been motivated to sterilize the respirable particles to prevent microbial growth in the packaged material with a reasonable expectation of success. The artisan

would be particularly motivated to sterilize the glucocorticosteroid in the form that it is intended to be used. It is noted that this rejection was previously overcome by the inclusion of a purity limitation. This claim has no such limitation.

The claim recites a product-by-process claim comprising "providing an unsterilized powder." Applicant states in the remarks that such a powder necessarily lacks the characteristics of a product that has been previously sterilized. One such characteristic is the presence of irradiation by-products. This limitation would only preclude the use of irradiation if such by-products could only be generated by irradiation.

Double Patenting

Claims 94-100 are again rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,686,346 in view of RUBINFELD et al (US 5,824,668) and ANSEL et al (Pharmaceutical Dosage Forms and Drug delivery Systems, 1995), as set forth in the previous Office action. Claims 101, 102, 105, and 107-109 are rejected over claim 22. Claims 136-138 and 142-144 are rejected over claim 12.

Claims 94-101 are again rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,291,445 in view of RUBINFELD et al (US 5,824,668) and ANSEL et al (Pharmaceutical Dosage Forms and Drug delivery Systems, 1995), as set forth in the previous Office action. Claims 136-138 and 142-144 are rejected over claim 8.

Applicant's traversal of these rejections have been addressed above.

Applicant's amendment and submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on October 17, 2005 prompted the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Wednesday, or Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 872-9306.

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Leigh C. Maier

Leigh C. Maier
Primary Examiner
October 28, 2005